Exhibit “M”

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Anterior Colporrhaphy versus Transvaginal Mesh for Pelvic-Organ Prolapse

Daniel Altman, M.D., Ph.D., Tapio Väyrynen, M.D., Marie Ellström Engh, M.D., Ph.D., Susanne Axelsen, M.D., Ph.D., and Christian Falconer, M.D., Ph.D., for the Nordic Transvaginal Mesh Group*

ABSTRACT

BACKGROUND

The use of standardized mesh kits for repair of pelvic-organ prolapse has spread rapidly in recent years, but it is unclear whether this approach results in better outcomes than traditional colporrhaphy.

METHODS

In this multicenter, parallel-group, randomized, controlled trial, we compared the use of a trocar-guided, transvaginal polypropylene-mesh repair kit with traditional colporrhaphy in women with prolapse of the anterior vaginal wall (cystocele). The primary outcome was a composite of the objective anatomical designation of stage 0 (no prolapse) or 1 (position of the anterior vaginal wall more than 1 cm above the hymen), according to the Pelvic Organ Prolapse Quantification system, and the subjective absence of symptoms of vaginal bulging 12 months after the surgery.

RESULTS

Of 389 women who were randomly assigned to a study treatment, 200 underwent prolapse repair with the transvaginal mesh kit and 189 underwent traditional colporrhaphy. At 1 year, the primary outcome was significantly more common in the women treated with transvaginal mesh repair (60.8%) than in those who underwent colporrhaphy (34.5%) (absolute difference, 26.3 percentage points; 95% confidence interval, 15.6 to 37.0). The surgery lasted longer and the rates of intraoperative hemorrhage were higher in the mesh-repair group than in the colporrhaphy group ($P<0.001$ for both comparisons). Rates of bladder perforation were 3.5% in the mesh-repair group and 0.5% in the colporrhaphy group ($P=0.07$), and the respective rates of new stress urinary incontinence after surgery were 12.3% and 6.3% ($P=0.05$). Surgical reintervention to correct mesh exposure during follow-up occurred in 3.2% of 186 patients in the mesh-repair group.

CONCLUSIONS

As compared with anterior colporrhaphy, use of a standardized, trocar-guided mesh kit for cystocele repair resulted in higher short-term rates of successful treatment but also in higher rates of surgical complications and postoperative adverse events. (Funded by the Karolinska Institutet and Ethicon; ClinicalTrials.gov number, NCT00566917.)

From the Division of Obstetrics and Gynecology, Department of Clinical Science, Danderyd Hospital (D.A., C.F.), and the Department of Medical Epidemiology and Biostatistics (D.A.), Karolinska Institutet, Stockholm; the Department of Obstetrics and Gynecology, Hospital District of Helsinki and Uusimaa, Hyvinkää Hospital, Hyvinkää, Finland (T.V.); the Department of Obstetrics and Gynaecology, Akershus University Hospital, University of Oslo, Lørenskog, Norway (M.E.E.); and the Department of Obstetrics and Gynecology, Aarhus University Hospital, Skejby, Denmark (S.A.). Address reprint requests to Dr. Altman at the Department of Obstetrics and Gynecology, Danderyd Hospital, 182 88 Stockholm, Sweden, or at daniel.altman@ds.se or daniel.altman@ki.se.

*Members of the Nordic Transvaginal Mesh Group are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2011;364:1826-36.

Pelvic-organ prolapse, a condition characterized by a downward descent of the pelvic organs, causing the vagina to protrude,[1] afflicts millions of women worldwide and is increasingly recognized as a global burden on women's health.[2,3] In the United States alone, more than 300,000 surgeries for pelvic-organ prolapse are performed each year, of which anterior colporrhaphy for prolapse of the anterior vaginal wall (cystocele) is the single most common operation.[4] However, because the risk of recurrence is 40% or more with this procedure,[5-7] there has been great interest in innovative surgical techniques that may improve outcomes after cystocele repair. Yet the evaluation of complex interventions has not kept pace with the rapid development of novel invasive therapies that involve synthetic implants.[8] Several observational studies have shown lower failure rates after biomaterial-augmented surgery, as compared with the traditional repair of pelvic-organ prolapse, but data from randomized trials to support specific treatment recommendations are lacking.[9]

Standardized trocar-guided mesh kits are increasingly used in prolapse surgery, and the approach differs fundamentally from traditional colporrhaphy. These operations involve the use of metal trocars for placement of a synthetic mesh, which is standardized in shape and size, to support the vaginal walls. Despite their widespread use, none of the marketed kits have been comprehensively evaluated in comparative trials. We designed a multicenter, parallel-group, randomized trial to determine the efficacy and safety of transvaginal mesh repair for prolapse of the anterior vaginal wall, as compared with the current standard of care.

Methods

Patients

The trial was conducted at 53 hospitals throughout Sweden, Norway, Finland, and Denmark. (For a list of the participating centers, see the Supplementary Appendix, available with the full text of this article at NEJM.org.) From December 2007 through December 2008, patients were screened by the participating surgeons for prolapse of the anterior vaginal wall after self-referral or referral by their general practitioner or gynecologist. Patients were invited to participate if they were 18 years of age or older and presented with primary or recurrent prolapse of the anterior vaginal wall that was stage 2 or higher (according to the Pelvic Organ Prolapse Quantification [POP-Q] system) and with symptoms of vaginal bulging or pelvic heaviness. Exclusion criteria were previous cancer of any pelvic organ, systemic glucocorticoid treatment, insulin-treated diabetes, an inability to participate in study follow-up or to provide informed consent, or the need for concomitant surgery. Oral and written informed consent was obtained from all participants. The trial was conducted in accordance with the protocol (available at NEJM.org).[10]

The study was approved by the appropriate research ethics committees in each country. A data and safety monitoring committee reviewed the progress and safety of the study during the recruitment period.

Randomization

Patients were randomly assigned in a ratio of 1:1, with the use of balanced blocks of four, to either traditional colporrhaphy or trocar-guided transvaginal mesh repair. Randomization took place when the gynecologic surgeon called the coordinating center before the intervention. Patients were assigned to treatment according to a sequentially numbered randomization list in the order these calls were received, and they were not made aware of their assignment until the 1-year follow-up visit had been completed.

Study Design

The participants completed baseline questionnaires concerning demographic characteristics and medical history. Before surgery and at follow-up visits scheduled for 2 and 12 months after surgery, patients completed the Urogenital Distress Inventory (UDI).[11] The Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) was completed at baseline and at 1 year.[12] The UDI consists of three subscales (each ranging from 0 to 100, with a maximum summary score of 300) reflecting different aspects of urogenital dysfunction: irritative symptoms (UDI-I), obstructive discomfort (UDI-O), and stress symptoms (UDI-S); higher scores indicate greater dysfunction. PISQ-12 scores range from 0 to 48, with higher scores indicating better sexual function.[13] Staging of vaginal prolapse was determined with the use of the POP-Q system.[14] Postoperative examinations were performed by a gynecologist other than the operating surgeon, if possible. Dif-

ferences between the surgical incisions required for the two procedures meant that the examiners were aware of the assigned interventions, and the use of sham incisions to conceal the assignments was considered to be unethical.

The primary outcome was a composite of objective and subjective measures: POP-Q stage 0 or 1 of the anterior vaginal wall (i.e., point Ba, which represents the most distal point of the anterior vaginal wall in relation to the hymen) and a negative response to the question, "Do you experience a feeling of bulging or protrusion in the vaginal area?" (question 16 on the UDI). Secondary outcome measures included the individual components of the primary composite end point, surgical complications, adverse events related to the procedure, and patient-reported urogenital distress and sexual function.

The manufacturer of the mesh kit did not provide the products used in this trial and had no involvement in the study design, data collection and analysis, the writing of the manuscript, or the decision to submit the results for publication.

SURGICAL PROCEDURES

All surgeons were qualified to perform both interventions. The surgical procedures were standardized before initiation of the study and were performed in an identical manner across participating centers. Postmenopausal patients received preoperative and postoperative topical estrogen treatment. Details of the surgical procedures are provided in the Supplementary Appendix. All mesh procedures involved use of the Gynecare Prolift Anterior Pelvic Floor Repair System kit (Ethicon).[15] Placement of the mesh is shown in Figure 1 of the Supplementary Appendix.

STATISTICAL ANALYSIS

The statistical power calculation was based on a superiority assumption with a binary primary outcome. On the basis of a previous study,[16] we estimated that at least 149 patients were needed in each treatment group for 90% power to detect a 20% difference in the primary outcome measure, with a two-tailed type I error of 1%, at 1 year after surgery. The primary analysis used the full data set, and all results were based on observed outcomes without imputation of missing data. Baseline characteristics are presented as means ±SD for continuous variables and as frequencies for categorical variables. Continuous end points were evaluated with the use of analysis of covariance (ANCOVA), with group and baseline values for the dependent variable entered as independent variables in a model.

Categorical end points were analyzed with the use of Fisher's exact test and univariate logistic regression, with the treatment group as the only independent variable. To evaluate the robustness of the results, we performed an additional multivariate logistic-regression analysis with adjustments for the following prespecified baseline covariates: age, body-mass index, parity, and presence or absence of a history of surgery for anterior-wall prolapse. In a post hoc analysis, we adjusted for the effects of descensus of the vaginal apex by adding the baseline position of POP-Q point C (the position of the vaginal apex before surgery) (numerical value) to the covariates. Results of the logistic-regression analyses are presented as odds ratios with 95% confidence intervals. Subsequent analyses included both a per-protocol analysis and a conservative sensitivity analysis of the binary primary outcome. For purposes of the sensitivity analysis, we assumed a worst-case scenario for the mesh-repair group (i.e., for all patients with missing data in the mesh-repair group, the study treatment was considered to be unsuccessful, whereas for patients with missing data in the colporrhaphy group, the study treatment was considered to be successful). All analyses were performed by an independent statistician who was unaware of the treatment assignments until data analysis for the primary end point had been completed.

RESULTS

STUDY POPULATION

A total of 1685 women were screened for enrollment, of whom 389 women were randomly assigned to treatment. Figure 1 shows the disposition of patients. Rates of nonadherence to the treatment assignment were low and were similar in the two treatment groups (3.7% for the colporrhaphy group and 4.5% for the mesh-repair group, P=0.80). Baseline characteristics and scores on the UDI and PISQ-12 were similar in the two groups (Table 1). Of the 389 patients, 61 (15.7%) underwent surgery as a secondary procedure because of prolapse recurrence. The 58 surgeons who participated in the trial performed a median of 3 of each of the two types of procedures (range, 1 to 8 for the mesh repair and 1 to 9 for colporrhaphy).

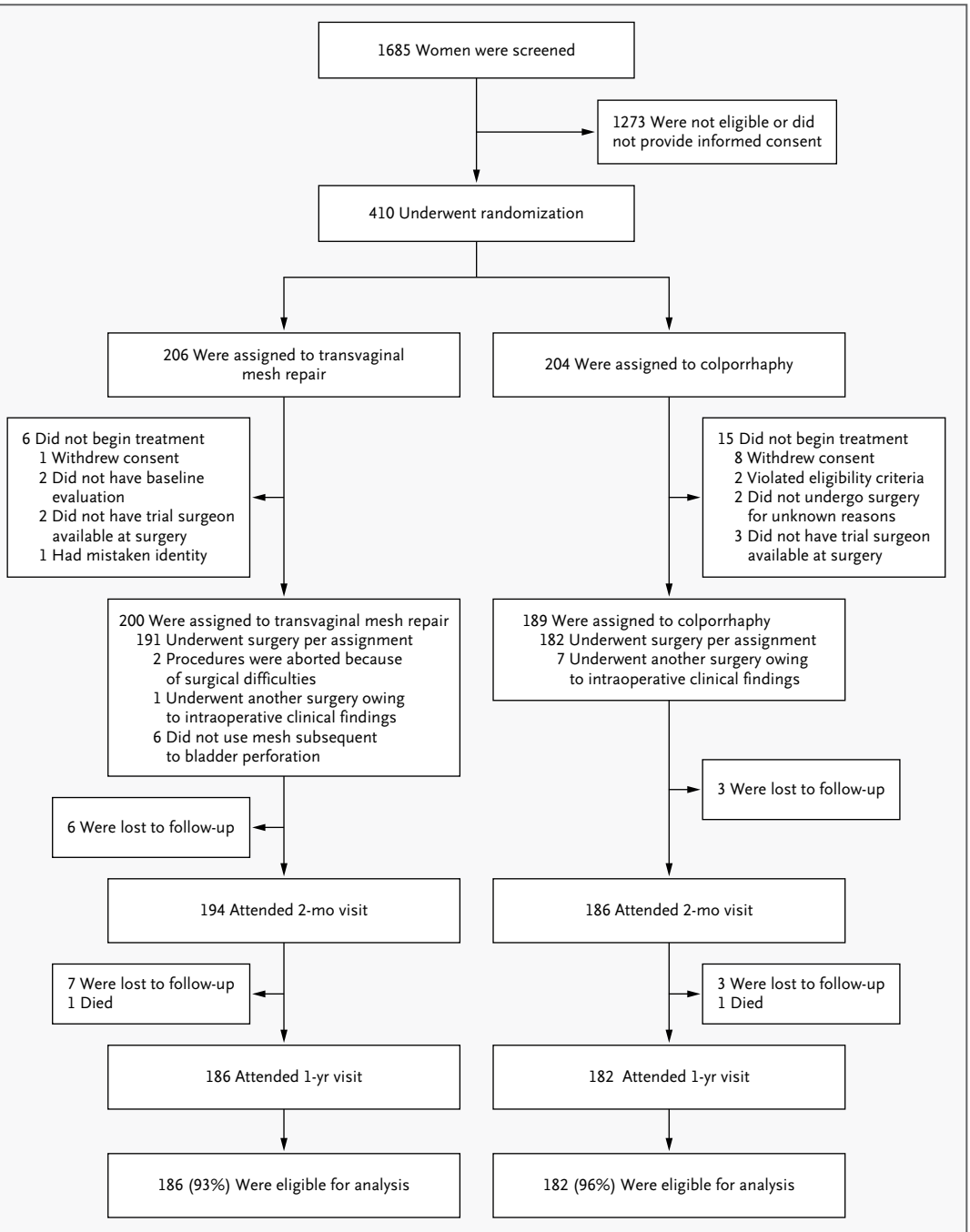

Figure 1. Randomization and Follow-up of the Study Patients.

OUTCOME MEASURES

One year after surgery, the primary outcome (i.e., no prolapse on the basis of both objective and subjective assessments) was significantly more common among patients in the mesh-repair group than among those in the colporrhaphy group (60.8% vs. 34.5%, P<0.001; adjusted odds ratio, 3.6; 95% confidence interval [CI], 2.2 to 5.9) (Tables 2 and 3). The result of the per-protocol analysis was similar to that of the intention-to-treat analysis (adjusted odds ratio, 4.3; 95% CI, 2.6 to 7.2). Mesh repair remained superior to colporrhaphy with re-

Table 1. Baseline Characteristics of the 389 Study Patients.*

Characteristic	Colporrhaphy Group (N=189)	Mesh-Repair Group (N=200)
Age at surgery — yr	65.1 (±9.8)	64.3 (±9.8)
Educational level reached — no. of patients (%)		
High school or equivalent	134 (70.9)	146 (73.0)
College or university	43 (22.8)	43 (21.5)
Parity		
Median	2	2
Range	0–7	0–6
Cesarean deliveries — no. of patients (%)	13 (6.9)	11 (5.5)
Current smokers — no. of patients (%)	22 (11.6)	25 (12.5)
Body-mass index	25.0 (±3.0)	26.2 (±3.4)
Age at menopause — yr	50.0 (±4.6)	50.3 (±4.8)
Current use of hormone therapy — no. of patients (%)	105 (55.6)	113 (56.5)
Previous surgery for cystocele — no. of patients (%)†	28 (14.8)	33 (16.5)
Prior pelvic surgery — no. of patients (%)		
Posterior prolapse repair	24 (12.7)	16 (8.0)
Hysterectomy	36 (19.0)	46 (23.0)
For incontinence	3 (1.6)	5 (2.5)
Salpingo-oophorectomy	4 (2.1)	3 (1.5)
Cervix amputation	1 (0.5)	3 (1.5)
Sacrospinal fixation	1 (0.5)	1 (0.5)
UDI‡	91.5 (±52.5)	86.9 (±48.2)
UDI-I	34.0 (±22.0)	34.0 (±20.5)
UDI-S	26.5 (±25.9)	23.4 (±23.5)
UDI-O	31.6 (±18.3)	32.0 (±18.5)
Symptom of vaginal bulging — no. of patients (%)§	158 (83.6)	169 (84.5)
POP-Q stage — no. of patients (%)¶		
2	103 (54.5)	99 (50.0)
3	83 (43.9)	99 (50.0)
Sexually active — no. of patients (%)	73 (38.6)	80 (40.0)
PISQ-12‖	33.1 (±6.7)	32.2 (±7.2)

* Plus–minus values are means ±SD.
† None of the patients had previously undergone pelvic reconstructive surgery that involved biomaterial implants.
‡ Scores on the Urogenital Distress Inventory (UDI) range from 0 to 300, with higher scores indicating greater distress (or "bother"). The maximum summary score is 100 for the UDI subscales, which include irritative symptoms (UDI-I), stress symptoms (UDI-S), and obstructive discomfort (UDI-O). The UDI scores have been combined to result in overall scores presented as means ±SD.
§ This symptom is part of the composite primary outcome measure and represents question 16 of the UDI.
¶ In stage 2 of the Pelvic Organ Prolapse Quantification (POP-Q) system, the anterior vaginal wall (adjacent to the bladder) descends to at least 1 cm above the hymen but not more than 1 cm below it; in stage 3, the anterior vaginal wall descends more than 1 cm below the hymen but less than the total length of the vagina. Baseline data were missing for three patients.
‖ Scores on the short-form Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) range from 0 to 48, with higher scores indicating better sexual function.

spect to the primary outcome in a sensitivity analysis that involved imputing outcomes that were disadvantageous for mesh repair (adjusted odds ratio, 2.1; 95% CI, 1.4 to 3.3). Adding the preoperative position of point C (vaginal apex) to the analysis had only a minor effect on the rate of treatment success for transvaginal mesh repair as compared with colporrhaphy (adjusted odds ratio,

Table 2. Primary and Secondary Outcome Measures after Colporrhaphy versus Mesh Repair for Anterior Vaginal-Wall Prolapse.

Outcome Measure	Colporrhaphy Group (N=189)	Mesh-Repair Group (N=200)	Treatment Effect (95% CI)*	P Value
			percentage points	
Successful composite primary outcome — no. of patients/total no. (%)†				
At 2 mo	88/178 (49.4)	138/190 (72.6)	23.2 (12.9 to 33.4)	<0.001
At 1 yr	60/174 (34.5)	107/176 (60.8)	26.3 (15.6 to 37.0)	<0.001
Prolapse stage 0 or 1 — no. of patients/total no. (%)				
At 2 mo	113/186 (60.8)	170/194 (87.6)	26.8 (17.9 to 35.8)	<0.001
At 1 yr	87/183 (47.5)	153/186 (82.3)	34.8 (25.1 to 44.3)	<0.001
No symptom of vaginal bulge — no. of patients/total no. (%)				
At 2 mo	136/178 (76.4)	159/193 (82.4)	6 (–2.8 to 14.8)	0.16
At 1 yr	108/174 (62.1)	135/179 (75.4)	13.3 (3.2 to 23.5)	0.008
UDI summary score — mean (95% CI)‡				
At 2 mo	41.2 (34.1 to 48.3)	51.2 (44.1 to 58.2)	10.0 (–0.01 to 20.0)	0.05
At 1 yr	53.6 (45.9 to 61.2)	53.6 (45.9 to 61.2)	0.03 (–10.8 to 10.8)	0.99
UDI-I subscale — mean (95% CI)				
At 2 mo	17.2 (14.6 to 19.9)	20.9 (18.4 to 23.5)	3.67 (0.0 to 7.4)	0.05
At 1 yr	23.2 (20.4 to 26.0)	22.2 (19.5 to 24.9)	–1.0 (–4.9 to 2.9)	0.62
UDI-S subscale — mean (95% CI)				
At 2 mo	17.6 (13.7 to 21.4)	24.3 (20.4 to 28.1)	6.71 (1.3 to 12.2)	0.02
At 1 yr	17.7 (13.9 to 21.4)	24.2 (20.5 to 28.0)	6.6 (1.3 to 11.9)	0.02
UDI-O subscale — mean (95% CI)				
At 2 mo	7.3 (5.7 to 9.0)	8.3 (6.6 to 9.9)	0.9 (–1.4 to 3.4)	0.43
At 1 yr	12.3 (10.3 to 14.3)	8.7 (6.7 to 10.7)	–3.6 (–6.4 to –0.8)	0.01
PISQ-12 summary score — mean (95% CI)§				
At 1 yr	35.1 (33.7 to 36.4)	35.0 (33.7 to 36.4)	–0.01 (–1.9 to 1.9)	0.99

* Treatment effect refers to difference between proportions or the mean difference between the colporrhaphy group and the mesh-repair group on the basis of the analysis of covariance model. CI denotes confidence interval.
† The primary composite outcome measure was defined as a combination of Pelvic Organ Prolapse Quantification (POP-Q) stage 0 or 1 (i.e., the anterior vaginal wall is positioned more than 1 cm above the hymen) and the absence of patient-reported vaginal bulging.
‡ Responses to the Urogenital Distress Inventory (UDI) questionnaire were combined to form overall scores; higher scores indicate more severe symptoms of distress. The maximum score is 300 for the UDI (with each subscale having a total score of 100). The three subscales of the UDI reflect different domains of urogenital dysfunction: irritative symptoms (UDI-I), stress symptoms (UDI-S), and obstructive discomfort (UDI-O).
§ Responses on the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) were combined to form an overall score (maximum score = 48); higher scores indicate better sexual function.

3.1; 95% CI, 1.9 to 5.2). There were no significant interactions detected for differences in treatment effects between the two procedures 1 year after surgery in relation to baseline patient characteristics (Table 3).

In secondary analyses performed to assess the two components of the primary outcome separately, use of the transvaginal mesh kit was superior to colporrhaphy with regard to the percentage of women in whom support of the anterior vaginal wall was restored to POP-Q stage 0 or 1 (82.3% vs. 47.5%, P<0.001) and the percentage of those who had symptoms of vaginal bulging (75.4% vs. 62.1%, P=0.008) at 1 year (Table 2). Detailed POP-Q results are provided in Table 1 in the Supplementary Appendix.

Between the 2-month and 1-year follow-up visits, UDI scores deteriorated in both treatment groups, although more notably in the colporrhaphy group. At the 1-year assessment, symptoms of stress urinary incontinence were significantly more bothersome in the mesh-repair group than in the

Table 3. Odds of Treatment Success for Primary Outcome in Relation to Baseline Characteristics at 1 Year after Surgery.*

Variable	Colporrhaphy Group (N=189	Mesh-Repair Group (N=200)	Treatment Effect† (95% CI)	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)‡	P Value for Interaction
	no. of patients (%)					
All patients	60/174 (34.5)	107/176 (60.8)	26.3 (15.6 to 37.0)	2.9 (1.9 to 4.6)	3.6 (2.2 to 5.9)	
Age at operation						
32–58 yr	14/45 (31.1)	27/48 (56.2)	25.1 (3.5 to 46.8)	2.8 (1.2 to 6.8)	2.6 (1.1 to 6.5)	0.80
59–64 yr	16/43 (37.2)	28/47 (59.6)	22.4 (0.0 to 44.7)	2.5 (1.1 to 5.9)	2.6 (1.1 to 6.3)	
65–71 yr	18/44 (40.9)	28/40 (70.0)	29.1 (6.4 to 51.8)	3.4 (1.4 to 8.6)	3.4 (1.4 to 8.9)	
72–91 yr	12/42 (28.6)	24/41 (58.5)	29.9 (7.2 to 52.7)	3.5 (1.4 to 9.0)	4.2 (1.6 to 11.3)	
Body-mass index§						
<25	31/86 (36.0)	43/58 (74.1)	38.1 (21.5 to 54.7)	5.1 (2.5 to 10.9)	5.1 (2.5 to 11.1)	0.53
25–30	21/58 (36.2)	46/78 (59.0)	22.8 (4.8 to 40.8)	2.5 (1.3 to 5.2)	2.8 (1.4 to 5.8)	
>30	3/13 (23.1)	8/20 (40.0)	16.9 (–20.8 to 54.7)	2.2 (0.5 to 12.3)	5.0 (0.7 to 58.5)	
Parity						
≤1 childbirth	7/18 (38.9)	12/25 (48.0)	9.1 (–25.5 to 43.7)	1.5 (0.4 to 5.1)	3.1 (0.6 to 18.7)	0.23
≥2 childbirths	51/151 (33.8)	93/149 (62.4)	28.6 (17.1 to 40.1)	3.3 (2.0 to 5.3)	3.8 (2.3 to 6.4)	
No previous anterior vaginal-wall repair	55/149 (36.9)	93/148 (62.8)	25.9 (14.3 to 37.6)	2.9 (1.8 to 4.7)	3.3 (2.0 to 5.6)	0.63
Recurrent anterior vaginal-wall prolapse	5/25 (20.0)	14/28 (50.0)	30 (1.9 to 58.1)	4.0 (1.2 to 14.8)	5.9 (1.6 to 26.8)	
Previous pelvic-floor surgery						
No	37/115 (32.2)	69/106 (65.1)	32.9 (19.6 to 46.3)	3.9 (2.3 to 6.9)	4.5 (2.4 to 8.7)	0.10
Yes	23/59 (39.0)	38/70 (54.3)	15.3 (–3.3 to 33.9)	1.9 (0.9 to 3.8)	2.9 (1.3 to 6.8)	
Previous hysterectomy						
No	49/140 (35.0)	83/134 (61.9)	26.9 (14.8 to 39.1)	3.0 (1.9 to 5.0)	3.6 (2.1 to 6.3)	0.88
Yes	11/34 (32.4)	24/42 (57.1)	24.7 (0.4 to 49.2)	2.8 (1.1 to 7.4)	4.6 (1.5 to 15.7)	
Prolapse at baseline						
Stage 2	40/95 (42.1)	54/87 (62.1)	20 (4.6 to 35.3)	2.2 (1.2 to 4.1)	2.7 (1.4 to 5.4)	0.09
Stage 3	18/77 (23.4)	52/87 (59.8)	36.4 (21.2 to 51.6)	4.9 (2.5 to 9.8)	7.0 (3.3 to 16.2)	

* Treatment success for the primary outcome was defined as Pelvic Organ Prolapse Quantification (POP-Q) stage 0 or 1 (i.e., the anterior vaginal wall is positioned more than 1 cm above the hymen) and the absence of patient-reported vaginal bulging. Each row in the table indicates the result of a distinct logistic-regression analysis. CI denotes confidence interval.
† Treatment effect is the difference (in percentage points) between the colporrhaphy group and the mesh-repair group.
‡ The analysis was adjusted for age, body-mass index, number of childbirths, and previous repair of the anterior vaginal wall unless the variable was the subgroup-defining variable.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

colporrhaphy group (P=0.02), whereas obstructive symptoms were less bothersome (P=0.01); there were no significant between-group differences in irritative symptoms at 1 year. New stress urinary incontinence occurred in 11 of 176 patients (6.2%) in the colporrhaphy group versus 22 of 179 (12.3%) in the mesh-repair group (P=0.05).

At 1 year, the mean PISQ-12 scores were modestly improved as compared with baseline scores and were similar in the two groups (Table 2). When we analyzed individual outcomes that might be affected differently after the two types of interventions, pain during sexual intercourse was reported to occur "usually" or "always" by 2% of the women after colporrhaphy and by 7.3% after transvaginal mesh surgery (P=0.07). When the patients were asked how satisfied they were with their sexual relationships with their partners, 40% of the colporrhaphy group and 48% of the mesh-repair group answered "usually" or "always" (P=0.37).

ADVERSE EVENTS

The mesh-repair group, as compared with the colporrhaphy group, had a significantly longer mean duration of surgery (52.6 vs. 33.5 minutes, P<0.001), greater mean intraoperative blood loss (84.7 vs. 35.4 ml, P<0.001), and more frequent need for intraoperative cystoscopy (P=0.006) (Table 4). More bladder perforations occurred in the mesh-repair group than in the colporrhaphy group (7 vs. 1, P=0.07). In the mesh-repair group, one patient had pelvic hemorrhage with blood loss in excess of 1000 ml, and blood loss exceeded 500 ml in four other patients. Inguinal pain and bladder-emptying difficulties during the hospital stay were more common after mesh repair than after colporrhaphy (P=0.06 for pain and P=0.05 for urine retention).

Adverse events during the first 2 months of follow-up were generally transient, and urinary tract infections, pelvic pain, and urine retention predominated. Five patients in the mesh-repair group reported severe pelvic pain at 2 months as compared with one patient in the colporrhaphy group (P=0.22); in all except one of these patients (who was in the mesh-repair group), the pain had resolved spontaneously by the 1-year follow-up visit. At 12 months, 5 of 186 patients in the mesh-repair group (2.7%) had undergone surgery for stress incontinence (P=0.06), and 6 (3.2%) had undergone vaginal wound revision (in all cases to correct mesh exposure) (P=0.03). One patient (in the colporrhaphy group) underwent a second anterior repair for prolapse recurrence. Two deaths (one in each treatment group) occurred during the follow-up period (at 5 and 10 months postoperatively), and both were attributed to cardiovascular disease.

DISCUSSION

In this randomized, controlled trial, use of a standardized trocar-guided mesh kit for cystocele repair, as compared with traditional anterior colporrhaphy, resulted in a higher success rate, on the basis of a composite of objective and subjective outcomes, and a lower risk of prolapse recurrence. The favorable main treatment effect of the transvaginal mesh repair was observed at both 2 months and 1 year postoperatively and persisted even after the imputation of missing data to the disadvantage of the mesh kit. Nevertheless, use of the trocar-guided mesh kit also resulted in higher rates of adverse events, including bladder perforations, pelvic hemorrhage, and mesh-related complications. Our results highlight the need for a careful evaluation of surgical innovations,[16,17] which are often widely adopted in the absence of data from clinical trials.

It is difficult to compare the anatomical and functional outcomes in our study with those reported in other randomized trials, owing to differences in surgical procedures, implant materials, and outcome measures.[5-7,18,19] Nonetheless, the majority of studies suggest that the use of synthetic mesh for cystocele repair decreases the risk of recurrence.[20] The anatomical success rates in our trial were similar to those in other studies with similar follow-up periods: 79 to 95% for trocar-guided transvaginal mesh[15,16,21,22] and 30 to 60% for colporrhaphy.[5-7] Not surprisingly, our success rates were lower for both surgical techniques when the assessment combined objective and subjective measures and applied a strict binary definition of success. Theoretically, the placement of a permanent mesh implant may be particularly useful in women whose native vaginal tissues are of "poor quality" (i.e., those with recurrent or advanced stages of prolapse).[23-25] Analyses of these factors and other baseline patient characteristics showed no significant interactions with the study treatment, although the statistical power of these analyses was limited.

The trocar-guided mesh kit creates a trampoline-like suspension of the anterior vaginal wall, which may overcorrect the position of the bladder neck and urethra, resulting in stress urinary incontinence. We found higher scores for stress incontinence and a higher frequency of new stress incontinence after the transvaginal mesh procedure, as compared with colporrhaphy. These results are consistent with urodynamic studies showing significantly lower maximal urethral closing pressures after use of a transvaginal mesh kit, as compared with colporrhaphy.[26] It is important for patients to understand this risk, since patients who are prepared for the possibility of adverse effects have a higher degree of satisfaction, regardless of the objective outcomes.[27] Other aspects of lower urinary tract function improved after transvaginal mesh surgery, as evidenced by lower scores for bothersome obstructive symptoms, as compared with the scores after colporrhaphy. Effects of the procedures on irritative symptoms were similar in the two treatment groups.

Other studies have yielded conflicting results with respect to sexual dysfunction after surgery with the use of a trocar-guided mesh kit, with some studies showing an increased risk of dyspareunia,[28] and others showing no change[29] or an improvement in this symptom.[30] However, these studies were underpowered or limited by a lack of controls. We found an increase in dyspareunia after the use of trocar-guided mesh repair, as compared with colporrhaphy, although overall reported satisfaction with sexual life was similar in the two treatment groups.[29]

The rate of serious surgical complications attributed to the mesh kit in our trial (4%) was similar to the rates in earlier multicenter studies (3.4% and 4.4%).[16,17] The longer duration of surgery, more frequent use of intraoperative cystoscopy, and greater frequency of bladder perforations and pel-

Table 4. Surgical Characteristics and Adverse Events for the Colporrhaphy and Mesh-Repair Groups.*

Variable	Colporrhaphy Group (N=189)	Mesh-Repair Group (N=200)	P Value†
Surgical procedure other than allocated — no. of patients (%)	7 (3.7)	9 (4.5)	0.80
Surgical characteristics			
General anesthesia — no. of patients (%)	58 (30.7)	83 (41.5)	0.03
Regional anesthesia — no. of patients (%)	98 (51.8)	115 (57.5)	0.31
Local anesthesia — no. of patients (%)	31 (16.4)	11 (5.5)	0.001
Operation time — min	33.5 (±10.5)	52.6 (±16.5)	<0.001
Estimated blood loss — ml	35.4 (±35.4)	84.7 (±163.5)	<0.001
Complications during surgery — no. of patients (%)			
Bladder perforation	1 (0.5)	7 (3.5)	0.07
Blood loss in excess of 500 ml	0	4 (2.0)	0.12
Blood loss in excess of 1000 ml	0	1 (0.5)	1.00
Intraoperative cystoscopy	1 (0.5)	11 (5.5)	0.006
Intraoperative ventricular fibrillation	0	1 (0.5)	0.49
Hospital stay — days	1.6 (±1.1)	1.8 (±1.2)	0.07
Adverse events during hospital stay — no. of patients (%)			
Inguinal pain‡	0	5 (2.5)	0.06
Urinary tract infection	4 (2.1)	4 (2.0)	1.00
Cardiovascular disease§	2 (1.1)	3 (1.5)	1.00
Anemia	0	1 (0.5)	1.00
Infection of unclear origin	0	1 (0.5)	1.00
Retropubic hematoma	0	1 (0.5)	1.00
Bladder-emptying difficulties	6 (3.2)	16 (8.0)	0.05
Catheter after hospital stay	0	2 (1.0)	0.50
Vaginal reoperation	0	2 (1.0)	0.50
Adverse events related to surgical procedure between hospital discharge and 2 mo — no. of patients (%)			
Urinary tract infections	4 (2.1)	8 (4.0)	0.38
Urinary retention treated with catheter	2 (1.1)	3 (1.5)	1.00
Vaginal wound bleeding	1 (0.5)	1 (0.5)	1.00
Vaginal dehiscence	1 (0.5)	1 (0.5)	1.00
Pelvic or genital pain‡	1 (0.5)	5 (2.5)	0.22
Other event	3 (1.6)	2 (1.0)	0.68

Table 4. (Continued.)

Variable	Colporrhaphy Group (N=189)	Mesh-Repair Group (N=200)	P Value†
Adverse events related to surgical procedure between 2 mo and 1 yr — no. of patients (%)			
Urinary tract infections	1 (0.5)	3 (1.5)	0.62
Surgery for stress urinary incontinence	0	5 (2.5)	0.06
Surgery for prolapse recurrence	1 (0.5)	0	0.49
Revision of vaginal wound for mesh exposure	0	6 (3.0)	0.03
Pelvic or genital pain‡	0	1 (0.5)	1.00
Deaths¶	1 (0.5)	1 (0.5)	1.00

* Plus–minus values are means ±SD.
† P values were calculated with the use of Fisher's exact test.
‡ During the initial hospital stay, information on inguinal pain was systematically obtained by means of a standardized set of questions to the surgeon. At 2 months and 1 year, information on adverse events that occurred between the two follow-up visits was systematically queried with the use of standardized questionnaires received from the patients.
§ This category included one case of hypotension and one case of angina in the colporrhaphy group and two cases of tachycardia and one case of chest palpitations in the mesh-repair group.
¶ Two patients died during follow-up, one in each treatment group. Both deaths were attributed to cardiovascular disease, which occurred at 5 months (in an 87-year-old patient in the colporrhaphy group) and at 10 months (in an 83-year-old patient in the mesh-repair group) after surgery.

vic hemorrhage associated with mesh repair in our study are consistent with the more invasive nature of this procedure as compared with colporrhaphy. Surgery to address mesh complications was reported in 3% of the women randomly assigned to the mesh procedure. This is higher than the complication rates reported after the use of midurethral sling procedures for incontinence[31] but lower than in another study of the use of transvaginal mesh for prolapse surgery.[22] Although the study populations may not be directly comparable, the low rate of mesh complications in our trial may be attributed at least in part to the antibiotic prophylaxis and local estrogen therapy provided to the patients and the supervised training sessions for all participating surgeons. Patients should understand, however, that the use of mesh may cause complications even after the immediate postoperative period.

Our study had some limitations. The postoperative assessors were aware of the treatment assignments, and it is possible that the surgeons' beliefs about mesh kits influenced their assessments. However, the observation that patients' subjective ratings were also better in the mesh group than in the colporrhaphy group supports the main results. Although the vaginal apex is often involved in large cystoceles,[32] anterior mesh kits are not intended to suspend the vaginal apex but rather to support the anterior vaginal wall.[33] The apparent lack of effect of apical descensus on the outcomes after cystocele repair may reflect the small number of patients in our trial who had clinically significant prolapse of the upper vagina and should be interpreted with caution.

In summary, use of a standardized trocar-guided transvaginal mesh kit resulted in a significantly higher rate of treatment success than did traditional colporrhaphy for repair of anterior vaginal-wall prolapse. When one is counseling patients regarding surgical options, the benefits of the mesh kit must be balanced against the higher rates of surgical complications and postoperative adverse events associated with this approach.

Supported by grants from the Swedish Society of Medicine, the Karolinska Institutet research foundations, the regional agreement on clinical research (ALF) between the Stockholm County Council and the Karolinska Institutet, and Ethicon.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Marcus Thuresson, Ph.D., at Statisticon, Uppsala, Sweden, for assistance with the statistical analyses.

REFERENCES

1. Jelovsek JE, Maher C, Barber MD. Pelvic organ prolapse. Lancet 2007;369:1027-38.
2. Kenton K, Mueller ER. The global burden of female pelvic floor disorders. BJU Int 2006;98:Suppl 1:1-5.
3. Gunasekera P, Sazaki J, Walker G. Pelvic organ prolapse: don't forget developing countries. Lancet 2007;369:1789-90.

4. Shah AD, Kohli N, Rajan SS, Hoyte L. The age distribution, rates, and types of surgery for pelvic organ prolapse in the U.S. Int Urogynecol J Pelvic Floor Dysfunct 2008;19:421-8.
5. Weber AM, Walters MD, Piedmonte MR, Ballard LA. Anterior colporrhaphy: a randomized trial of three surgical techniques. Am J Obstet Gynecol 2001;185:1299-304.
6. Sand PK, Koduri S, Lobel RW, et al. Prospective randomized trial of polyglactin 910 mesh to prevent recurrence of cystoceles and rectoceles. Am J Obstet Gynecol 2001;184:1357-62.
7. Nguyen JN, Burchette RJ. Outcome after anterior vaginal prolapse repair: a randomized controlled trial. Obstet Gynecol 2008;111:891-8.
8. McCulloch P, Altman DG, Campbell WB, et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet 2009;374:1105-12.
9. Sung VW, Rogers RG, Schaffer JI, et al. Graft use in transvaginal pelvic organ prolapse repair: a systematic review. Obstet Gynecol 2008;112:1131-42.
10. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c869.
11. Shumaker SA, Wyman JF, Uebersax JS, McClish D, Fantl JA. Health-related quality of life measures for women with urinary incontinence: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Qual Life Res 1994;3:291-306.
12. Rogers RG, Coates KW, Kammerer-Doak D, Khalsa S, Qualls C. A short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12). Int Urogynecol J Pelvic Floor Dysfunct 2003;14:164-8. [Erratum, Int Urogynecol J Pelvic Floor Dysfunct 2004;15:219.]
13. FitzGerald MP, Kenton K, Shott S, Brubaker L. Responsiveness of quality of life measurements to change after reconstructive pelvic surgery. Am J Obstet Gynecol 2001;185:20-4. [Erratum, Am J Obstet Gynecol 2001;185:1278.]
14. Bump RC, Mattiasson A, Bø K, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol 1996;175:10-7.
15. Fatton B, Amblard J, Debodinance P, Cosson M, Jacquetin B. Transvaginal repair of genital prolapse: preliminary results of a new tension-free vaginal mesh (Prolift technique) — a case series multicentric study. Int Urogynecol J Pelvic Floor Dysfunct 2007;18:743-52.
16. Elmér C, Altman D, Engh ME, Axelsen S, Vayrynen T, Falconer C. Trocar-guided transvaginal mesh repair of pelvic organ prolapse. Obstet Gynecol 2009;113:117-26.
17. Altman D, Falconer C. Perioperative morbidity using transvaginal mesh in pelvic organ prolapse repair. Obstet Gynecol 2007;109:303-8.
18. Meschia M, Pifarotti P, Bernasconi F, Magatti F, Riva D, Kocjancic E. Porcine skin collagen implants to prevent anterior vaginal wall prolapse recurrence: a multicenter, randomized study. J Urol 2007;177:192-5.
19. Hiltunen R, Nieminen K, Takala T, et al. Low-weight polypropylene mesh for anterior vaginal wall prolapse: a randomized controlled trial. Obstet Gynecol 2007;110:455-62.
20. Maher C, Feiner B, Baessler K, Adams EJ, Hagen S, Glazener CM. Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev 2010;4:CD004014.
21. Abdel-Fattah M, Ramsay I. Retrospective multicentre study of the new minimally invasive mesh repair devices for pelvic organ prolapse. BJOG 2008;115:22-30.
22. Feiner B, Jelovsek JE, Maher C. Efficacy and safety of transvaginal mesh kits in the treatment of prolapse of the vaginal apex: a systematic review. BJOG 2009;116:15-24.
23. Brincat M, Moniz CF, Studd JW, Darby AJ, Magos A, Cooper D. Sex hormones and skin collagen content in postmenopausal women. Br Med J (Clin Res Ed) 1986;287:1337-8.
24. Jackson SR, Avery NC, Tarlton JF, Eckford SD, Abrams P, Bailey AJ. Changes in metabolism of collagen in genitourinary prolapse. Lancet 1996;347:1658-61.
25. DeLancey JO. Anatomic aspects of vaginal eversion after hysterectomy. Am J Obstet Gynecol 1992;166:1717-24.
26. Ek M, Tegerstedt G, Falconer C, et al. Urodynamic assessment of anterior vaginal wall surgery: a randomized comparison between colporraphy and transvaginal mesh. Neurourol Urodyn 2010;29:527-31.
27. Kenton K, Pham T, Mueller E, Brubaker L. Patient preparedness: an important predictor of surgical outcome. Am J Obstet Gynecol 2007;197(6):654.e1-654.e6.
28. de Tayrac R, Deffieux X, Gervaise A, Chauveaud-Lambling A, Fernandez H. Long-term anatomical and functional assessment of trans-vaginal cystocele repair using a tension-free polypropylene mesh. Int Urogynecol J Pelvic Floor Dysfunct 2006;17:483-8.
29. Altman D, Elmér C, Kiilholma P, Kinne I, Tegerstedt G, Falconer C. Sexual dysfunction after trocar-guided transvaginal mesh repair of pelvic organ prolapse. Obstet Gynecol 2009;113:127-33.
30. Sentilhes L, Berthier A, Sergent F, Verspyck E, Descamps P, Marpeau L. Sexual function in women before and after transvaginal mesh repair for pelvic organ prolapse. Int Urogynecol J Pelvic Floor Dysfunct 2008;19:763-72.
31. Richter HE, Albo ME, Zyczynski HM, et al. Retropubic versus transobturator midurethral slings for stress incontinence. N Engl J Med 2010;362:2066-76.
32. Rooney K, Kenton K, Mueller ER, FitzGerald MP, Brubaker L. Advanced anterior vaginal wall prolapse is highly correlated with apical prolapse. Am J Obstet Gynecol 2006;195:1837-40.
33. Hinoul P, Jacquetin B. The total (not the anterior) vaginal mesh concept should be considered when apical vaginal support is the issue. Am J Obstet Gynecol 2010;202(4):e9-e10.